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3,557,106

2-[DI - (β-HYDROXY-LOWER ALKYL)AMINO]-4,7-DI - (HETEROCYCLIC AMINO) - 6 - PHENYL-PTERIDINES

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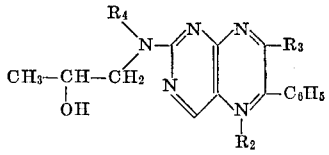
Int. Cl. C07d 57/28
U.S. Cl. 260—247.5 11 Claims

ABSTRACT OF THE DISCLOSURE

Compounds of the formula



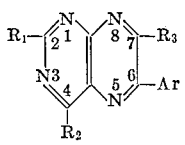
wherein

R_2 is morpholino or 2'-methyl-morpholino,
R_3 is pyrrolidino, piperidino, 3'-hydroxy-piperidino morpholino, or 2'-methylmorpholino, and
R_4 is β-hydroxy-ethyl or β-hydroxy-n-propyl, useful as coronary dilators in warm-blooded animals.

U.S. Pat. 2,940,972 discloses 2,4,6,7-tetra-substituted pteridines, where one of the substituents is a nitrogen-containing heterocyclic ring, two of the other substituents are substituted or unsubstituted amino or a nitrogen-containing heterocyclic ring, and the fourth substituent is substituted or unsubstituted amino, a nitrogen-containing heterocyclic ring, hydrogen, halogen, alkyl, aralkyl, aryl, substituted or unsubstituted hydroxyl, or substituted or unsubstituted mercapto. These compounds are disclosed to exhibit coronary-dilating, antipyretic, analgesic and sedative activties.

This invention relates to novel 2,4,6,7-tetra-substituted pteridines as well as to various methods of preparing these compounds.

More particularly, the present invention relates to tetra-substituted pteridines of the formula



(I)

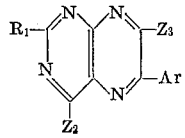
wherein

Ar is phenyl, halo-phenyl, nitro-phenyl, hydroxy-phenyl, lower alkyl-phenyl or lower alkoxy-phenyl,
R_1 is di-lower alkyl-amino, alkyl-cycloalkyl-amino or alkyl-aralkyl-amino, each having one or more hydroxyl substituents attached to the hydrocarbon moiety, and
R_2 and R_3 are each pyrrolidino, hydroxy-pyrrolidino, lower alkyl-pyrrolidino, piperidino, hydroxy-piperidino, lower alkyl-piperadino, piperazino, hydroxy-piperazino, lower alkyl-piperazino, morpholino or lower alkyl-morpholino.

The compounds according to the present invention may be prepared by a number of different methods involving well known chemical principles, among which the following have proved to be particularly convenient and efficient:

Method A

By reacting a compound of the formula

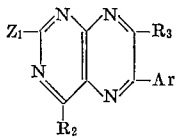


(II)

wherein Ar and R_1 have the same meanings as in Formula I and Z_2 and Z_3, which may be identical to or different from each other, are halogen, substituted hydroxyl or substituted mercapto, although one of them may already have a meaning ascribed to R_2 and R_3 in Formula I, with amines of the formulas R_2H and R_3H wherein R_2 and R_3, which may be identical to or different from each other, have the same meanings as in Formula I.

Method B

By reacting a compound of the formula



(III)

wherein Ar, R_2 and R_3 have the same meanings as in Formula I and Z_1 is halogen, substituted hydroxyl or substituted mercapto, with an amine of the formula R_1H wherein R_1 has the same meanings as in Formula I.

The reactions of methods A and B are carried out at a temperature between room temperature and 220° C., if desired in the presence of an acid-binding agent and of an inert solvent. The selection of the proper reaction temperature depends mainly upon the nature of substituents Z_1, Z_2 and Z_3 as well as upon the reactivity of the amines R_1H, R_2H and R_3H. If Z_1, Z_2 or Z_3 are halogen, only moderately elevated reaction temperatures are required to replace them by R_1, R_2 or R_3, respectively. On the other hand, if Z_1, Z_2 or Z_3 are substituted hydroxyl or substituted mercapto, the replacement reaction requires higher reaction temperatures; in some instances it is advantageous to add a reaction accelerator, preferably a copper salt or a salt formed by the amine reaction component with an acid, or to perform the reaction in a closed vessel.

In those cases where Z_1, Z_2 and Z_3 are substituted hydroxyl or substituted mercapto, the substituents may be lower alkyl, aralkyl or aryl.

The solvent medium for the reaction may be any desired inert organic solvent, such as acetone, benzene, dioxane or dimethylformamide.

The acid-binding agent may be an inorganic or tertiary organic base, such as an alkali metal hydroxide, an alkali metal carbonate or a trialkylamine; or also one or more of the amine reaction components R_1H, R_2H and R_3H, provided they are present in sufficient excess over and above the amount stoichiometrically required to react with the pteridine compound II or III. If present in sufficient quantity, the amine reaction components may also serve as the solvent medium for the reaction.

If method A is used to replace Z_2 and Z_3 with R_2 and R_3 which are identical to each other, the reaction mixture must contain at least two mols of the amine reactant per mol of pteridine compound II. On the other hand, if method A is used to replace Z_2 and Z_3 with R_2 and R_3 which are different from each other, the reaction may be performed stepwise as follows: If Z_2 and Z_3 are identical, for instance, if both are halogen, Z_2 is replaced first by R_2, and then in a second reaction step Z_3 is replaced by R_3; on the other hand, if Z_2 and Z_3 are not identical, for instance, if one is halogen and the other is substituted